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Conceptual DFT as a Helpful Chemoinformatics Tool for the Study of the Clavanin Family of Antimicrobial Marine Peptides

Norma Flores-Holguín, Juan Frau
and Daniel Glossman-Mitnik

Abstract

A well-behaved model chemistry previously validated for the study of the chemical reactivity of peptides was considered for the calculation of the molecular properties and structures of the clavanin family of antimicrobial marine peptides. A methodology based on conceptual density functional theory (CDFT) was chosen for the determination of the reactivity descriptors. The molecular active sites were associated with the active regions of the molecules related to the nucleophilic and electrophilic Fukui functions. Finally, the drug-likenesses and the bioactivity scores for the clavanin peptides were predicted through a homology methodology relating them with the calculated reactivity descriptors, while other properties like the pKas were determined following a methodology developed by our group.

Keywords: clavanin, conceptual DFT, chemical reactivity, drug-likeness features, bioactivity scores

1. Introduction

Bioactive peptides are promising novel drug leads that may fill the gap between small molecules and larger biologicals. This is reflected by a multitude of recent peptide discovery and development approaches. However, their use as therapeutic lead molecules is challenged by their typically poor stability and lack of oral bio-availability. This is often due to the linear nature of peptides that not only exhibit free ends but multiple cleavage sites that are readily recognized by enzymes that degrade peptide chains into inactive fragments or single amino acids [1–10].

The marine environment is considered Earth's last frontier of exploration. In fact, a common belief is that just less than 5% of the vast and rich marine environment has been explored. Our seas and oceans represent a very unknown resource for the discovery of novel organisms, (bio)products, (bio)processes, and for the development of bioinspired synthetic drugs. Recent advances in genetics and other (bio)molecular techniques are providing all necessary tools to access these still-untapped marine resources on a larger scale and, consequently, enable exploitation of the true promise of the blue biotechnology [11].

Clavanins are α-helical antimicrobial peptides isolated from a mixed tunicate population of *Styela clava* hemocytes. Clavanin A, VFQFLGKIIH10HVGNFVHGFS 20HVFa, and the clavanins BE are 23-peptide antibiotics containing 18 identical residues bearing a C-terminally amidated amino acid moiety [12].

This study seeks to assess the molecular properties such as the chemical reactivity and bioactivity scores through the application of the conceptual density functional theory (CDFT) concepts. Understanding the reactivity properties of the clavanin family of antimicrobial peptides is important in the use of Fukui functions to represent the peptide reactivity with the molecular systems in the process of developing new drugs. Bioavailability and bioactivity scores of the molecular systems will also be compared with the descriptors of the conceptual density functional theory [13–16].

2. Computational methodology

The generation of 3D structures and the proposition of their respective low-energy conformers in the prediction and calculation of the properties of the five members of the clavanin family of antimicrobial peptides in this study was carried out using ChemAxon Calculator Plugins. In the process of geometry optimization, the molecules with the lowest energy conformation were used, while the DFTBA program was used in the optimization of the rest of the conformers. The MN12SX/Def2TZVP/H20 model chemistry was used in the re-optimization of the five conformers having the lowest energy. Consequently, the real minimum approach was used in the confirmation of the optimized clavanin structures through the application of the vibrational frequency analysis technique. The process of calculating the electronic properties for the chemical reactivity of the antimicrobial peptides involved the use of MN12SX/Def2TZVP/H2O model chemistry through the optimized molecular structures.

3. Results and discussion

ChemAxon Calculator Plugins were used in the process of deriving the molecular structures and the bioactivity properties of the conformers. The optimization and re-optimization of the conformers was carried out using the DFTBA program and the MN12SX/DefTZVP/H20 model chemistry, respectively, as explained in the Computational Methodology section [17]. The graphical sketches of the molecular structures of the clavanins A–E are shown in **Figure 1**. The density functional tight-binding method was used in the re-optimization of the molecular structures, while the MN12SX density functional method combined with the SMD solvent model and the DefTZVP were used in the second optimization of the molecular structures. The MN12SX/DefTZVP/H20 model chemistry was used in determining the electronic properties of each molecular structure after using calculation analysis procedures to determine whether all the molecular structures correspond to their respective minimum energy requirements. According to Becke, a common misconception exists in the connection of the electronic ground states and the adiabatic connection since the superiority of the Kohn-Sham (or KS) model is not recognized due to its minimum molecular energy [18]. Baerends et al. state that the level of energy excitation within a KS system is used as an effective measure of the optimization to the molecular optical gap [19]. Thus, the HOMO-LUMO gap of the KS model is used to approximate the excitation energy within the KS model based on which is a basic requirement in determining the consistency with the molecular structures [20].
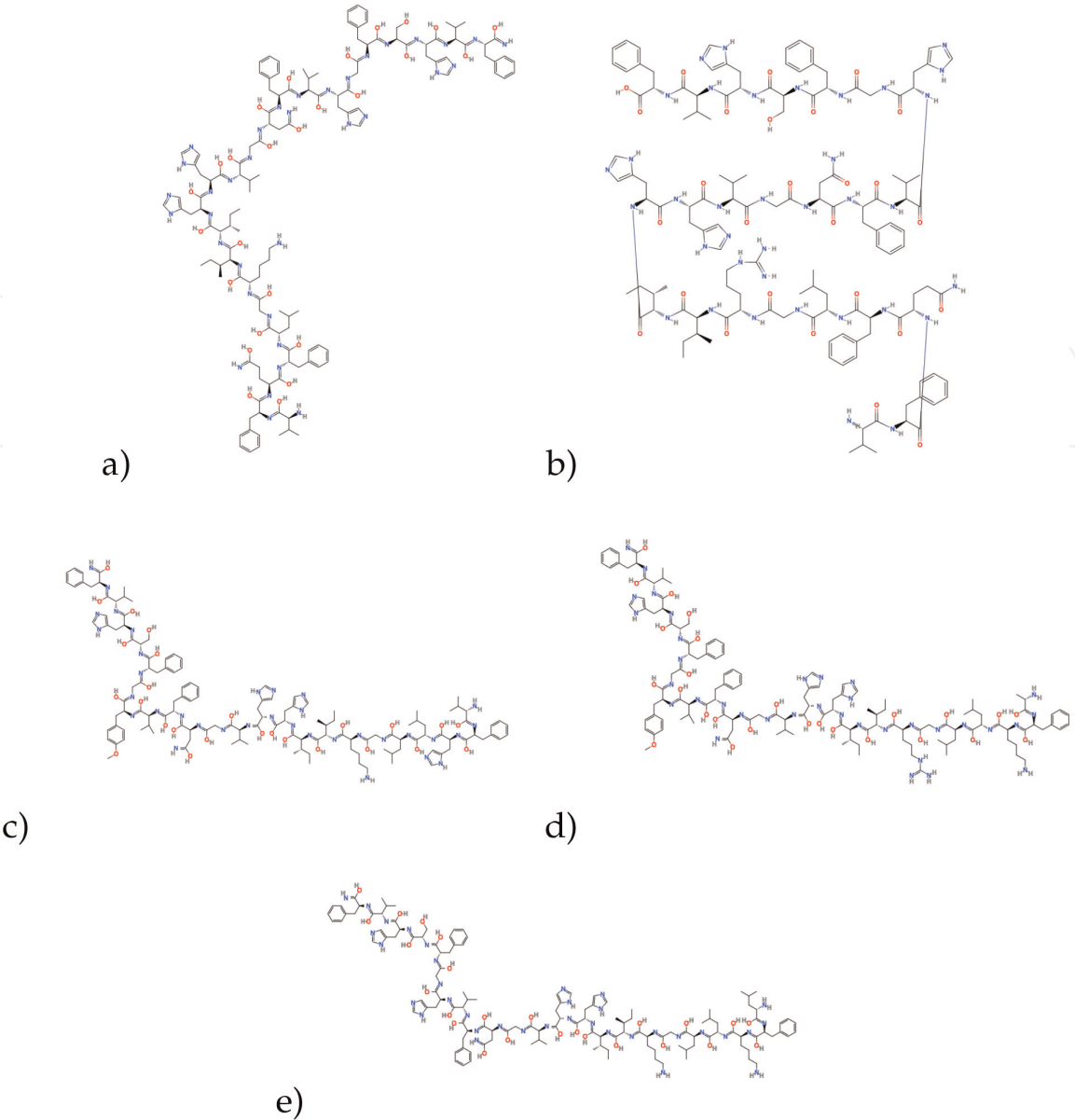
Figure 1.
Graphical representation of the optimized molecular structures of the marine antimicrobial peptides of the clavanin family: (a) Clavanin A, (b) Clavanin B, (c) Clavanin C, (d) Clavanin D, and (e) Clavanin E.

Ground state calculations are used in determining the optimal maximum absorption wavelength that belongs to the marine peptides of the clavanin family based on the predetermined density functional to find the respective λ_{max} values through the application of theoretical models to establish the HOMO-LUMO gaps.

Therefore, the calculation of the maximum wavelength absorption of the clavanins A–E antimicrobial peptides involved conducting ground-state calculations with the aforementioned density functional at the same level of model chemistry and theory and determining the HOMO-LUMO gap.

The amino acid sequences for the Clavanins A–E are shown as follows [21]:

	10	20	
Clavanin A	VFQFLGKIIH	HVGNFVHGFS	HVF
Clavanin B	VFQFLGRIIH	HVGNFVHGFS	HVF
Clavanin C	VFHLLGKIIH	HVGNFVYGFS	HVF
Clavanin D	AFKLLGRIIH	HVGNFVYGFS	HVF
Clavanin E	LFKLLGKIIH	HVGNFVHGFS	HVF

The calculated electronic properties, namely, the total electronic energy, the energies of the HOMO and LUMO orbitals, and the maximum absorption wavelength (in nm) calculated on the basis of the HOMO-LUMO gap of the ground state and determined by using the MN12SX/Def2TZVP/H2O model chemistry are presented in **Table 1**.

3.1 Calculation of global reactivity descriptors

According to Frau and Glossman-Mitnik, the evaluation of marine peptides and melanoidins in the generation of HOMO and LUMO energies is required in the verification of the levels of agreement with the estimated Koopmans' theorem based on the combination of the MN12SX density functional and the Def2TZVP basis set [22–28]. This justifies the application of the proposed KID (for Koopmans in DFT) technique.

Considering the KID technique used on the previous studies being integrated into the finite difference approximation [22–28], the following expressions can be used to define the global reactivity descriptors [15, 16, 29, 30]:

$$\text{Electronegativity } \chi = -\frac{1}{2}(I + A) \approx \frac{1}{2}(\varepsilon_L + \varepsilon_H) \tag{1}$$

$$\text{Global hardness } \eta = (I - A) \approx (\varepsilon_L - \varepsilon_H) \tag{2}$$

$$\text{Electrophilicity } \omega = \frac{\mu^2}{2\eta} = \frac{(I + A)^2}{4(I - A)} \approx \frac{(\varepsilon_L + \varepsilon_H)^2}{4(\varepsilon_L - \varepsilon_H)} \tag{3}$$

$$\text{Electrodonating power } \omega^- = \frac{(3I + A)^2}{16(I - A)} \approx \frac{(3\varepsilon_H + \varepsilon_L)^2}{16\eta} \tag{4}$$

$$\text{Electroaccepting power } \omega^+ = \frac{(I + 3A)^2}{16(I - A)} \approx \frac{(\varepsilon_H + 3\varepsilon_L)^2}{16\eta} \tag{5}$$

$$\text{Net electrophilicity } \Delta\omega^{\pm} = \omega^+ - (-\omega^-) = \omega^+ + \omega^- \tag{6}$$

where ε_H and ε_L are the HOMO and LUMO energies associated with each of the peptides.

The calculated values for these global reactivity descriptors using the MN12SX/Def2TZVP/H2O model chemistry and the associated HOMO and LUMO energies are displayed in **Table 2**.

	Total electronic energy	HOMO	LUMO	λ_{max}
Clavanin A	−8960.8018	−6.1098	−0.6329	226
Clavanin B	−9090.5934	−6.2148	−1.2218	248
Clavanin C	−8985.1955	−6.1046	−0.6697	228
Clavanin D	−8964.4080	−6.1623	−0.6776	226
Clavanin E	−8852.4122	−6.1231	−0.6555	227

Table 1.
Electronic energies of the neutral molecular systems (in au) of the clavanins A–E, the HOMO and LUMO orbital energies (in eV), and the maximum absorption wavelengths λ_{max} (nm) calculated with the MN12SX density functionals and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

3.2 Calculation of the pKa of the clavanins A–E peptides

The previous discussion focused on the application of the conceptual DFT descriptors to evaluate the computation prediction of the pKas peptides where it was established that the pKa = 16.3088–0.868 η relationship would play an important role in the initial prediction of complex peptides, which are important in the manufacture of medical drugs [31]. Given the biological level of pH, the peptides under study exist as neutral molecules and are still considered to be neutral during the pKa computations [31]. The pKa relationship is also important in the optimization of the molecular structure of every conformer as well as the computation of the pKa values for all molecules given the η values shown in **Table 2**. The computational results of the pKa values for the clavanin molecules are shown in **Table 3**.

The pKa values shown in **Table 3** indicate that the computational methodology used is effective in the differentiation of the respective pKa values for all the peptidic molecules irrespective of the significance of the difference. The pKa values of these peptides are important in the manufacture of pharmaceutical drugs by explaining the procedures used in drug delivery and their respective action mechanisms.

Molecule	Electronegativity	Global hardness	Electrophilicity
Clavanin A	3.3714	5.4768	1.0376
Clavanin B	3.7183	4.9930	1.3845
Clavanin C	3.3871	5.4349	1.0555
Clavanin D	3.4199	5.4847	1.0662
Clavanin E	3.3893	5.4676	1.0505
Molecule	**Electrodonating power**	**Electroaccepting power**	**Net electrophilicity**
Clavanin A	4.1033	0.7319	4.8352
Clavanin B	4.9402	1.2219	6.1622
Clavanin C	4.1442	0.7570	4.9012
Clavanin D	4.1852	0.7653	4.9505
Clavanin E	4.1374	0.7481	4.8855

Table 2.
Global reactivity descriptors of the clavanins A–E molecules calculated with the MN12SX/Def2TZVP/H2O model chemistry.

Molecule	pKa
Clavanin A	11.78
Clavanin B	12.18
Clavanin C	11.82
Clavanin D	11.77
Clavanin E	11.79

Table 3.
pKas of the clavanins A–E molecules.

3.3 Local reactivity descriptor calculation

Applying the same ideas as before, the definitions for the local reactivity descriptors will be [15]:

$$\text{Nucleophilic Fukui function} \, f^+(\mathbf{r}) = \rho_{N+1}(\mathbf{r}) - \rho_N(\mathbf{r}) \tag{7}$$

$$\text{Electrophilic Fukui function} \, f^-(\mathbf{r}) = \rho_N(\mathbf{r}) - \rho_{N-1}(\mathbf{r}) \tag{8}$$

which are relationships between the electronic densities of the neutral, positive, and negative species.

Clavanin A

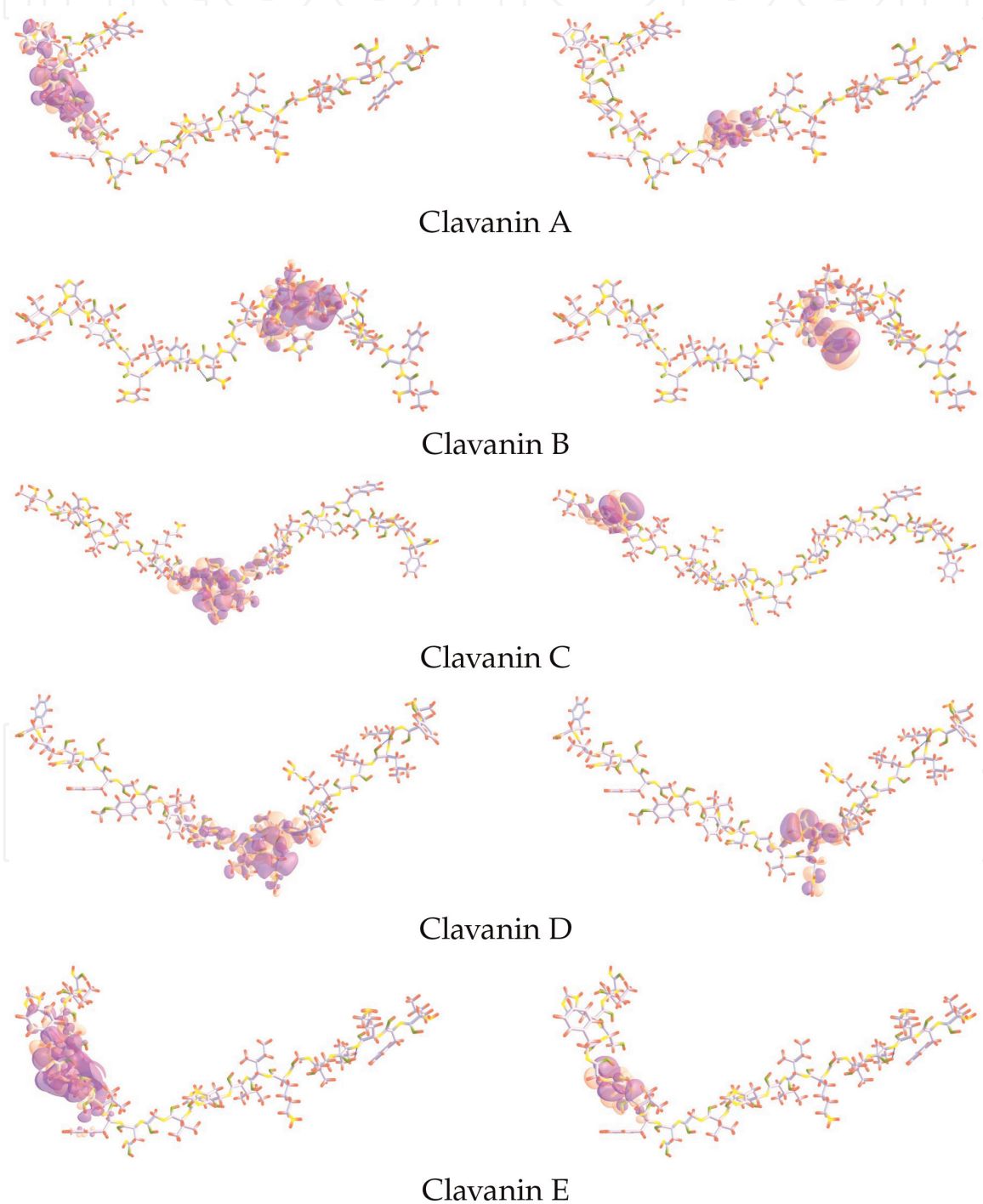Clavanin B

Clavanin C

Clavanin D

Clavanin E

Figure 2.
The right column represents the nucleophilic Fukui function $f^+(\mathbf{r})$, while the left column represents the electrophilic Fukui function $f^-(\mathbf{r})$ of five antimicrobial peptides of marine origin belonging to the clavanin family.

The electrophilic Fukui functions $f^-(\mathbf{r})$ and nucleophilic Fukui functions $f^+(\mathbf{r})$ for the clavanin A–E molecules are shown in **Figure 2**.

3.4 Bioavailability and bioactivity scores

According to Leeson et al., it is important to check the species level of compliance of a potential therapeutic drug to the Lipinski rule of five, which explains whether the compound contains certain drug properties [32]. Molinspiration and MolSoft software were used to compute the molecular drug properties in a compound as shown in **Table 4** given that miLogP is a representation of the water partition coefficient. The rate of violations of the Lipinski rule of five is measured using nviol, while TPSA represents the polar surface area of the molecule. The hydrogen bond donors and the hydrogen bond acceptors are represented by nOHNH and nON, respectively.

Table 4 shows the application of the Lipinski rule of five in the calculation of the molecular properties of the antimicrobial marine peptides of the clavanin family. Volume represents the molecular volume of the peptides, while MW represents the molecular weight of the peptides.

The degree of oral bioavailability of the marine molecules that can be potentially used in the manufacture of drugs is measured using the Lipinski rule of five by determining the molecules that possess drug-like properties. However, this technique cannot be applied in measuring the bioavailability of the peptides due to the existence of hydrogen bonds and molecular weight properties as shown in **Table 4**.

This study applied a different technique in the evaluation of the chemical structure of other compounds that were predicted to possess similar pharmacological properties as the clavanin peptides under study. As illustrated in the Computational Methodology section, the evaluation of the pharmacological properties of different compounds in the process of determining the bioactivity scores can be carried out using Molinspiration software based on the variability of the drug targets as shown in **Table 5**. According to the table, the organic molecules whose bioactivity score is less than zero are considered to be active, while the organic molecules whose bioactivity score are between zero and negative five are considered to be moderately active, and the organic molecules with a score of less than negative five are considered to be inactive. All peptides that were studied during this study were found to have moderate bioactivity scores with respect to enzymatic reactivity.

Property	Clavanin A	Clavanin B	Clavanin C	Clavanin D	Clavanin E
miLogP	−0.95	−4.49	−1.18	−0.23	−0.30
TPSA	1036.27	986.53	1001.42	1034.64	1018.21
natoms	192	194	193	192	190
nON	61	63	60	61	60
nOHNH	38	37	35	38	37
Nviol	3	3	3	3	3
Nrotb	83	84	83	85	85
Volume	2460.93	2477.80	2489.31	2483.28	2470.86
MW	2666.14	2695.14	2681.20	2672.19	2646.19

Table 4.
Molecular properties of the clavanins A–E peptides calculated to verify the Lipinski rule of five.

Property	Clavanin A	Clavanin B	Clavanin C	Clavanin D	Clavanin E
GPCR ligand	−4.18	−4.17	−4.18	−4.17	−4.17
Ion channel Modulator	−4.19	−4.18	−4.19	−4.18	−4.18
Kinase inhibitor	−4.20	−4.20	−4.20	−4.20	−4.19
Nuclear receptor ligand	−4.21	−4.21	−4.21	−4.21	−4.21
Protease inhibitor	−4.17	−4.15	−4.18	−4.16	−4.17
Enzyme inhibitor	−4.18	−4.17	−4.17	−4.20	−4.17

Table 5.
Bioactivity scores of the clavanins A–E peptides.

Table 5 shows the bioactivity scores of the clavanin family of antimicrobial marine peptides based on the interactions with various enzyme inhibitors, GPCR ligand, the protease inhibitors, the ion channel modulators, the kinase inhibitors, and the nuclear receptors.

4. Conclusions

Along this research, the chemical reactivity of a group of five members of the clavanin family of marine antimicrobial peptides was studied by resorting to the conceptual DFT as a tool to explain the molecular interactions.

The information about the global and local reactivity descriptors of the antimicrobial peptides acquired in this work could be helpful to assist in the design of new pharmaceutical drugs based on these compounds.

Among the many descriptors that could be useful for the development of new medicines, the pKa is of paramount importance because it is related to the water solubility of drugs. Thus, when the experimental values of the pKa are unknown, the approximate QSAR relationship employed in this work could be a useful predictive tool for the determination of the pKas of small and large peptides.

Finally, the molecular properties related to bioavailability have been predicted using different methodologies already described in the literature, and the descriptors used for the quantification of the bioactivity allowed the characterization of the studied peptides.

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Conflict of interest

The authors declare no conflict of interest.

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